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A STEREOSELECTIVE TOTAL SYNTHESIS OF (±)-SATIVENE

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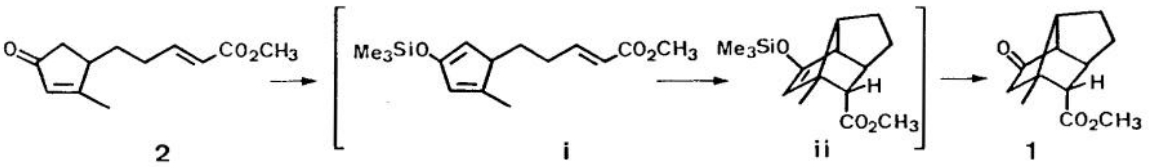
Abstract: (±)-Sativene (3) is stereoselectively synthesised from tricyclic ketoester 1 in 32% overall yield.

The formation, in 94% yield, of the tricyclic ketoester 1 from the (3-alkenyl)-cyclopentenone 2 has been described[1]. This reaction is believed to proceed *via* the regio- and stereospecific intramolecular [4+2] cycloaddition of the silylenol ether (i) formed *in situ*; the cycloadduct, tricyclic silylenol ether (ii), unstable under the conditions of its formation, then leads directly to 1, see Scheme 1. The present letter describes an application of this novel transformation to a total synthesis of the racemate of the naturally occurring sesquiterpene sativene (3)[2], see Scheme 2.

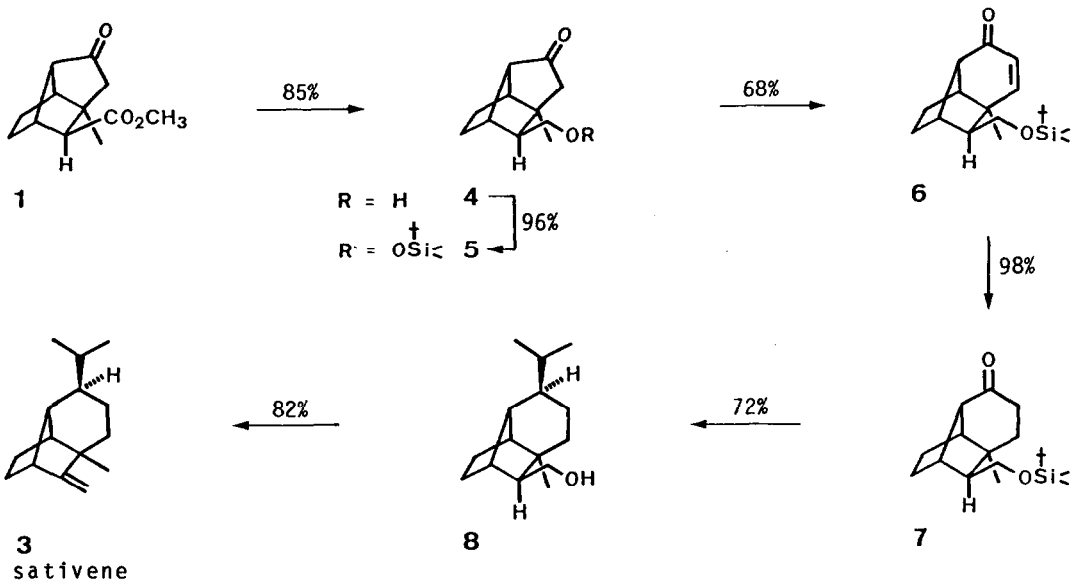
Scheme 1



2 i ii 1

Protection of the ketone group in 1 by ketalisation ($HOCH_2CH_2OH/H^+$), reduction of the ester functionality ($LiAlH_4/Et_2O$) and deprotection (H_3O^+) gave hydroxyketone 4 (mp 137 - 138°) in 85% yield (from 2), which was converted to its *t*-butyldimethylsilyl ether 5 (mp 42 - 43°, 96%). Regiospecific one-carbon ring expansion of 5 was now effected by carbene addition[3] (Zn-Cu couple/CH_2I_2/Et_2O/reflux) to the trimethylsilylenol ether of 5 (prepared under kinetically-controlled conditions: LDA/THF/-78° then Me_3SiCl), followed by regiospecific opening of the resulting cyclopropane ring[4] ($FeCl_3$/DMF-pyridine/0 - 20°, 2 h) to provide tricyclic ketone 6 (mp 74 - 75°) in 68% yield. Hydrogenation (5% Pd-C/H_2 (1 atm) /EtOH) smoothly gave ketone 7 (mp 57 - 58°, 98%) which was transformed to the primary alcohol 8 in 72% yield, in three steps: Wittig reaction[5] ($KH/Me_2\overset{+}{C}HP\overset{-}{Ph_3}I$/toluene-DMSO (9 : 1)/60°, 70 h, 79%), hydrogenation (PtO_2/H_2(1 atm)/AcOH-EtOAc (3 : 1)) and silyl ether cleavage (H_3O^+). Finally, the formation and subsequent elimination of the *o*-nitrophenylselenoxide[6] of 8 ($Bu_3P/o\text{-}O_2NArSeCN$/pyridine-THF then 30% H_2O_2) furnished (±)-sativene (3) in 82% yield. Structural confirmation was provided by analysis of the spectral data (IR, ^1H- and ^{13}C-NMR, MS) which were identical to those of synthetic (+)-sativene.

Scheme 2[7]



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References and Notes

1. See preceding paper.
2. For previous syntheses, see J.E. McMurry, J. Am. Chem. Soc., 90, 6821 (1968); J.E. McMurry, Tetrahedron Lett., 3731 (1970); G.L. Hodgson, D.F. MacSweeney and T. Money, J. Chem. Soc. Perkin I, 2113 (1973); C.R. Eck, G.L. Hodgson, D.F. MacSweeney, R.W. Mills and T. Money, *ibid.*, 1938 (1974); E. Piers, M.B. Geraghty, R.D. Smillie and M. Soucy, Can. J. Chem., 53, 2849 (1975); P. Bakuzis, O.O.S. Campos and M.L.F. Bakuzis, J. Org. Chem., 41, 3261 (1976); M. Yanagiya, K. Kaneko, T. Kaji and T. Matsumoto, Tetrahedron Lett., 1761 (1979).
3. R.J. Rawson and I.T. Harrison, J. Org. Chem., 35, 2057 (1970); S. Murai, T. Aya and N. Sonoda, *ibid.*, 38, 4354 (1973).
4. Y. Ito, S. Fujii and T. Saegusa, J. Org. Chem., 41, 2073 (1976).
5. Use of other Wittig conditions only gave traces of product.
6. K.B. Sharpless and M.W. Young, J. Org. Chem., 40, 947 (1975); P.A. Grieco, S. Gilman and M. Nishizawa, *ibid.*, 41, 1485 (1976).
7. All compounds give spectral data (IR, ^{1}H- and ^{13}C-NMR, MS) in accordance with their structures.

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